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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,011	06/08/2001	Loren J. Field	7037-440/IU-30-DIV-CON4	4537

7590 10/03/2002

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EXAMINER	
KETTER, JAMES S	
ART UNIT	PAPER NUMBER
1636	3

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,011	FIELD, LOREN J.	
	Examiner	Art Unit	
	James S. Ketter	1636	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-68 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-68 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be passed to issue.

No computer readable form (CRF) has been submitted for the instant application. Rather than submit a newly-prepared CRF, however, it is strongly suggested that Applicant submit a written request that the CRF from the parent file (09/441,315, issued as US Patent 6,399,300) be used to generate a CRF for the present Application.

Applicant is given the time period set for response to this Office Action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-12 of U.S. Patent No. 5,602,301. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because in each instance the claimed subject matter is drawn to an embodiment set forth explicitly in the specification of the patent. As such, the instant claims are not patentably distinct from the patented claims even though each instant claim may be of narrower scope than the respective patented claim. The instant application descends from the patent through a series of continuations and divisionals, and as such, necessarily shares the same disclosure.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the rejection:

The nature of the invention. The claimed invention encompasses an ex vivo gene therapy method, i.e., methods wherein the cells are transfected with a recombinant gene, and as such, the method must be therapeutically useable to be enabled.

The amount of direction or guidance presented in the specification, and the presence or absence of working examples.

The specification as filed teaches that some expression of a reporter gene construct is seen soon after the graft is implanted. Further, some angiogenic activity is detected in the heart tissue where TGF-beta was expressed. However, no actual showing of successful treatment of a defect is exemplified. Further, the actual level of expression of the TGF-beta gene was not shown to be therapeutically useful, nor was any determination of the persistence of expression made and disclosed. A brief listing of potentially useful proteins that might be expressed in the disclosed system is set forth at the paragraph bridging pages 9 and 10 of the specification. However, no discussion of what levels of expression of any proteins is offered. Furthermore, no teachings with respect to the number of cells to be implanted for any particular disease condition, nor teachings with respect to the location of such implantation or other factors relating to the surgical aspects of the invention, nor even teachings with respect to the use of any particular

expressed protein for any particular disease state, are set forth. These factors would have to be determined by trial-and-error methodology.

The state of the prior art, and the predictability or unpredictability of the art. Generally, the prior art had seen no successes in treatment methods of either the in vivo or the ex vivo type of gene therapy. Several reviews of the art are discussed below, which show that the problems of vector selection and, more importantly, persistence of predictable and useable levels of expression of the therapeutic protein, represented technical barriers to the practice of gene therapy methods. Verma et al. (U, newly cited) teaches, e.g., at the four paragraphs at page 240, starting with the paragraph bridging the left-hand and center columns, and ending with the second full paragraph at the right-hand column, that persistence of expression and adequate expression systems, i.e., enhancer-promoter combinations, were problematic in ex vivo gene therapy methods tried through that time. Furthermore, Table 2, at page 242, shows that none of the transfection systems extant at the time were suitable for actual treatment methods. Anderson (V, newly cited) sets forth the state of the art as of 1998. Specifically, Anderson makes clear that methods extant in the art, particularly vector selection, delivery methods and persistence of gene expression, were still inadequate to permit routine practice of the gene therapy, let alone any demonstrably successful practice at all. Both the first paragraph, left-hand column, at page 25 and the conclusory paragraphs at page 30 make clear that Anderson did not regard practice of gene therapy methods at all routine as of 1998.

The quantity of experimentation. It is clear from the art, as shown by Verma et al. or Anderson, cited above, that a very large amount experimentation had already been underway in the art as of 1997 and 1998. Even with that amount of work, no successful gene therapy methods

had been demonstrated. Both references acknowledge the need for more work as of those dates. See, e.g., Verma et al. at page 239, at the first two introductory paragraphs, and Anderson, e.g., at page 25, also at the first two introductory paragraphs, and the last two paragraphs at page 30.

The breadth of the claims. The instant claims are drawn to the treatment of a wide variety of disease states, and to a wide variety of protein to be expressed in such treatment. As such, the claims would have been regarded by one of skill as very broad.

Conclusion. Were the skilled practitioner to have attempted to practice the claimed gene therapy methods, said practitioner first would have turned first to the specification for guidance in selecting dosages, treatment regimens and other factors which may bear upon the success of such treatment. However, as set forth above, such guidance in the specification is limited in nature, and is insufficient with respect to prediction of proper levels of expression. Said practitioner then would have turned to the prior art to obtain detailed guidance for practice of the claimed methods. However, as set forth above, the prior art does not recognize any clearly successful gene therapy methods. Thus, the skilled practitioner would not have been able to find the necessary guidance in the prior art. Finally, said practitioner would have been forced to turn to empirical experimentation to determine appropriate dosages, treatment regimens and other factors, required for successful practice of a gene therapy method. However, as set forth above, the amount of experimentation recognized by the art as required for development of a successful gene therapy protocol is very large, and of a largely trial-and-error nature. Furthermore, as set forth above, the field of gene therapy is unpredictable. A large amount of experimentation in an unpredictable art with little or no available guidance is clearly undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claim recites "issue" in line 3. However, it would appear that "tissue" was intended.

Certain papers related to this application may be submitted to the directly to the Examiner by facsimile transmission at (703) 746-5155. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993)(see 37 CFR ' 1.6(d)). To send the facsimile to the Art Unit instead, the Art Unit 1636 Fax number is (703) 305-7939. NOTE: If Applicant does submit a paper by fax to this number, the Examiner must be notified promptly, to ensure matching of the faxed paper to the application file, and the original signed copy should be retained by Applicant or Applicant's representative. (703) 308-4242 or (703) 305-3014 may be used without notification of the Examiner, with such faxed papers being handled in the manner of mailed responses. Applicant is encouraged to use the latter two fax numbers unless immediate action by the Examiner is required, e.g., during discussions of claim language for allowable subject matter. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the Examiner with respect to the examination on the merits should be directed to James Ketter whose telephone number is (703) 308-1169. The Examiner normally can be reached on M-F (9:00-6:30), with alternate Fridays off.

Questions regarding formalities and processing of the case should be directed to Zeta Adams, whose telephone number is (703) 305-3291.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Remy Yucel, can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Jsk
September 27, 2002

JAMES KETTER
PRIMARY EXAMINER

Application No. 09/878,011

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing" OR REQUEST TO USE CRF FROM PARENT APPLICATION

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.